the Fox Chase Cancer Center (Philadelphia, Pa.), Dr. Pelayo Correa of the Louisiana State University (New Orleans), and Dr. Stephen Lagakos of the Harvard School of Public Health (Boston, Mass.), who served on the Data Safety and Monitoring Committee. We also acknowledge and thank Hoffmann-La Roche for assistance in the provision of the vitamin/mineral supplements.

Manuscript received February 19, 1993, revised June 22, 1993; accepted July 1, 1993.

Nutrition Intervention Trials in Linxian, China: Multiple Vitamin/Mineral Supplementation, Cancer Incidence, and Disease-Specific Mortality Among Adults With Esophageal Dysplasia

*Jun-Yao Li, Philip R. Taylor, Bing Li, Sanford Dawsey, Guo-Qing Wang, Abby G. Ershow, Wande Guo, Shu-Fan Liu, Chung S. Yang, Qiong Shen, Wen Wang, Steven D. Mark, Xiao-Nong Zou, Peter Greenwald, Yang-Ping Wu, William J. Blot**

Background: **A number of vitamins and minerals have been shown to influence carcinogenesis in experimental animals. In humans, epidemiologic evidence suggests that intake of fruits and vegetables may reduce risk of esophageal and other cancers. Vitamins and minerals in these foods may contribute to the reduced cancer risk. The people of Linxian, China, have persistently low intake of multiple nutrients and exhibit one of the world's highest rates of esophageal/gastric cardia cancer, with an exceptionally high risk of esophageal dysplasia.** ***Purpose:*** **To determine whether supplementation with multiple vitamins and minerals may reduce esophageal/gastric cardia cancer among persons with esophageal dysplasia, we conducted a 6-year prospective intervention trial in Linxian.** ***Methods:*** **Mortality and cancer incidence were ascertained from May 1985 through May 1991 for 3318 persons with cytologic evidence of esophageal dysplasia who were randomly assigned to receive, throughout that period, daily supplementation with 14 vitamins and 12 minerals or placebo. Doses were typically two to three times U.S. Recommended Daily Allowances. Compliance was assessed by counting unused pills monthly for all trial participants and by assaying nutrient levels in blood collected from samples of individuals randomly selected without replacement every 3 months throughout the trial. Cancers were identified through routine surveillance and by special cytology and endoscopy screenings after 2½ years and 6 years.** ***Results:*** **A total of 324 deaths occurred during the 6-year intervention period; 167 occurred in the control (placebo) group and 157 occurred in the supplement group. Cancer was the leading cause of death (54% of all deaths); 18% were due to cerebrovascular diseases and 29% to other causes. Cumulative esophageal/gastric cardia death rates were 8% lower (relative risk [RR] = 0.92; 95% confidence interval [CI] = 0.67-1.28) among individuals receiving supplements rather than placebo, a nonsignificant (*P*>.10) difference. Risk of total mortality was 7% lower (RR = 0.93; 95% CI = 0.75-1.16; *P*>.10), total cancer 4% lower (RR = 0.96; 95% CI = 0.71-1.29; *P*>.10), cerebrovascular disease 38% lower (RR = 0.62; 95% CI = 0.37-1.06; *P* = .08), and other diseases 12% higher (RR = 1.12; 95% CI = 0.74-1.69; *P*>.10) among the treated group. Cumulative cancer incidence rates were nearly the same in the two groups.** ***Conclusions:*** **No substantial short-term beneficial effect on incidence or mortality for this type of cancer occurred following daily supplementation with multiple vitamins and minerals among adults with precancerous lesions of the esophagus.** ***Implications:*** **Although no statistically significant short-term benefits were observed, longer follow-up should be more informative about the effectiveness of this 6-year supplementation on cancer and other diseases among individuals with esophageal dysplasia. [J Natl Cancer Inst 85:1492–1498, 1993]**

Rates of esophageal/gastric cardia cancer in Linxian, a rural county in Henan Province, north-central China, are among the highest in the world (*1*). The excess risk is especially pronounced among persons with esophageal dysplasia, a precancerous lesion affecting over 20% of adults in this area (*2,3*). The excess cancers occur not only as squamous cell carcinomas of the esophagus, but also as adenocarcinomas of the gastric cardia. Traditionally, both tumors have been called "esophageal cancer" in Linxian because of their proximity to one another and similarity in symptoms.

**See* "Notes" section following "References."

Reasons for the elevated rates of cancer in Linxian are unclear; no strong risk factors have been detected in observational studies (*4,5*). Epidemiologic and experimental evidence suggests, however, that diet and nutrition are related to risk of esophageal and stomach cancer, with increased risks among those with low intake of fresh vegetables and fruits (*6,7*). Intake of fresh fruits, meat, and other animal products has been limited in Linxian. Surveys in the 1970s and early 1980s (*8-11*) found low blood levels of multiple micronutrients.

The high rates of cancer, low dietary intake of several nutrients, and administrative considerations favorable for implementation of a large trial combined to make Linxian a desirable setting in which to test a cancer chemoprevention strategy. To test whether supplementation with vitamins and minerals might reduce the high rates of esophageal/gastric cardia cancer, we initiated two randomized trials (*12,13*) in this high-risk area. One trial, involving supplementation of the general population with specific vitamin/mineral combinations, is the subject of the previous article in this issue of the Journal (*13*). Here, we report the initial death and cancer results among individuals with cytologically diagnosed esophageal dysplasia who received daily supplementation with multiple vitamins and minerals for 6 years. Our primary objective was to evaluate the effect of the supplements on esophageal/gastric cardia cancer incidence and mortality.

Table 1. Daily doses and types of micronutrients in the supplements for dysplasia trial*

Vitamin/mineral	Compound	Dose
Beta carotene		15 mg
Vitamin A	Acetate	10000 IU
Vitamin E	Di-alpha tocopherol acetate	60 IU
Vitamin C	Ascorbic acid	180 mg
Folic acid		800 μg
Vitamin B_1	Thiamine mononitrate	5 mg
Vitamin B_2	Riboflavin	5.2 mg
Niacinamide		40 mg
Vitamin B_6	Pyridoxine HCl	6 mg
Vitamin B_{12}	Cyanocobalamin	18 μg
Vitamin D		800 IU
Biotin		90 μg
Pantothenic acid	Calcium pantothenate	20 mg
Calcium	Dibasic calcium phosphate	324 mg
Phosphorus	Dibasic calcium phosphate	250 mg
Iodine	Potassium iodide	300 μg
Iron	Ferrous fumarate	54 mg
Magnesium	Magnesium oxide	200 mg
Copper	Cupric oxide	6 mg
Manganese	Manganese sulfate	15 mg
Potassium	Potassium chloride	15.4 mg
Chloride	Potassium chloride	14 mg
Chromium	Chromium chloride	30 μg
Molybdenum	Sodium molybdate	30 μg
Selenium	Sodium selenate	50 μg
Zinc	Zinc sulfate	45 mg

*Participants received two multivitamin, multimineral tablets (Centrum; Lederle Laboratories, Inc.) and one beta carotene capsule (Solatene; Hoffmann-LaRoche, Inc.) or matching placebos daily.

Subjects and Methods

Participants were randomly assigned to supplements (multivitamin/mineral tablets or capsules) or matching placebos in a two-group design. This design was chosen because it was complementary to the factorial design used in the companion trial presented in this issue of the Journal (*13*), and it provided a cost-effective and simple means to test multiple nutrients simultaneously. It is, however, not informative regarding the effect of individual nutrients. Randomization was performed in blocks of 10 patients within strata defined by commune, gender, and age. The daily dose and type of micronutrients in the supplements are shown in Table 1 and included a total of 14 vitamins and 12 minerals. The doses were typically two to three times the U.S. Recommended Daily Allowances (RDAs), but ranged from 0.26 to seven times the RDA depending on the vitamin or mineral (*14*). Each subject was given three pills daily, including one capsule (beta carotene as Solatene [Hoffmann-LaRoche, Inc., Nutley, N.J.] or placebo) and two tablets (vitamin/mineral supplement as Centrum [Lederle Laboratories, Inc., Pearl River, N.Y.] or placebos).

Potential participants were eligible if they were between the ages of 40 and 69 years, lived in one of three northern Linxian communes (Yaocun, Rencun, or Donggang), provided consent, and had a diagnosis of esophageal dysplasia on a balloon cytology examination. Individuals were excluded if they were taking vitamins of any type regularly, had a history of malignancy or other debilitating disease, or were taking antitumor B, a traditional Chinese drug consisting of a mixture of six medicinal herbs. The diagnoses of esophageal dysplasia arose primarily from population-based esophageal balloon cytology examinations conducted in November and December 1983 (*2*). The examination involved the swallowing of a small balloon encased in a mesh net and connected to a narrow tube. The balloon was then inflated with a fixed volume of air and withdrawn through the esophagus. Finally, the balloon was smeared across glass slides for subsequent cytologic evaluation of dysplasia. Individuals diagnosed with dysplasia 1 (low-grade dysplasia) or dysplasia 2 (high-grade dysplasia) on the basis of Chinese cytology criteria (*2*) in this or other recent balloon examinations were invited to participate in the baseline screening phase of the intervention trial.

Baseline screening was performed from August to October of 1984 and included interviews to obtain demographic, lifestyle, risk factor, and health status information; physical examinations; and blood and toenail sample collections. Randomization occurred in November 1984. Pill delivery commenced at the beginning of May 1985 and continued through the end of April 1991, a total of 72 months.

A team of over 200 village doctors delivered two bottles of pills monthly to each participant in the trial. At the time of the visit, bottles from the previous month were collected, the remaining pills were counted and the data recorded, new pill bottles were dispensed, and participants were asked about side effects. Compliance was assessed by counting unused pills monthly for all trial participants and by assaying nutrient levels in blood collected from up to 36 individuals randomly selected without replacement every 3 months throughout the trial.

Incident cancers and deaths were identified through several methods that assured essentially complete ascertainment of these events among trial participants. All medical facilities in the three communes under study, plus the Linxian County Cancer Hospital and the cancer hospital in the prefecture capital of Anyang, provided rapid notice of all cancer diagnoses among residents of the communes in the trials. Participants with cancer symptoms and those who died from any cause were identified by village doctors on their monthly visits to deliver and retrieve pills. Additional visits to look for symptomatic individuals were made by a medical team from the Cancer Institute of the Chinese Academy of Medical Sciences in Beijing; this team was based at a field station at the Yaocun commune. Symptomatic individuals were referred to this field station or their commune hospital for further evaluation.

Cancers were also ascertained through repeat cytology examinations offered to all participants after 30 months of intervention (86% of subjects participated) and again at the cessation of pill delivery (78% of subjects participated). Additionally, endoscopic examinations were performed on up to one fourth of the subjects at these times. Approximately half of all esophageal and gastric cardia cancers were diagnosed through these cytologic and endoscopic screenings. Participation rates in these special screenings did not differ by treatment group. Diagnostic materials for 89% of the cancer cases were reviewed by a panel of Chinese and American experts in pathology, cytology, radiology, and gastroenterology. Parallel reviews were conducted by senior Chinese diagnosticians for the remaining cancer cases and for deaths due to causes other than cancer.

We compared rates of esophageal/gastric cardia cancer mortality and incidence during the 6-year intervention period among those receiving vitamin/mineral supplements versus placebo. Rates were also calculated for other cancer mortality and incidence, other causes of death, and total mortality. The relative risks (RRs) for end points were estimated using Cox proportional hazards and logistic regression models (*15*). All RRs and confidence intervals (CIs) presented for the effect of being in the treatment versus the placebo group were adjusted for the stratifying factors of age, sex, and commune. They were also adjusted for initial grade of dysplasia, since slightly but significantly (P = .02) more persons in the treatment group had grade 2 (high-grade) dysplasia.

Results

Among the approximately 3700 potentially eligible participants, 1% refused to participate, 4% were out of the area, 1% were too sick, and 1% did not join the trial for other reasons. In addition, 2% were excluded due to self-reported cancer at screening or death or diagnosis of cancer prior to the start of intervention (*12*).

Participant characteristics by group are shown in Table 2. The median age of participants at the start of intervention in 1985 was 54. Approximately one fourth had dysplasia 2, and 43% reported a family history in first-degree relatives of either esophageal or stomach cancer. There were no statistically significant differences between the randomized groups with respect to any of the subject characteristics examined except for the grade of cytologic dysplasia from the 1983 balloon screening. Individuals randomly assigned to supplements had a 3% higher prevalence of dysplasia 2 in this examination than those assigned to the placebo group.

Compliance assessed by monthly pill counts indicated that for 87% in the placebo group and 89% in the supplement group, pill disappearance exceeded 90%. Only 4% in each group were poor compliers (i.e., <50% pill disappearance). The overall pill disappearance rate was 94% in both groups, with only a slight decline (from 96% in year 1 to 92% in year 6 in both groups) over the duration of the trial.

Compliance assessed biochemically over the 6-year intervention is shown in Table 3. None of the nutrient levels differed between the two randomized groups at baseline. In contrast, all values were significantly (P = .0001) different in the supplement group compared with the placebo group throughout the intervention period.

A total of 324 deaths occurred during the period May 1985 to April 1991 among trial participants (Table 4). Cancer was the leading cause, accounting for 176 deaths (54%), followed by cerebrovascular disease (57 deaths; 18%) and other causes (91 deaths; 29%), none of which contributed more than 5% of all deaths (data not shown).

Table 2. Dysplasia trial participant characteristics by treatment group

	Group			
Participant characteristic	No., placebo group	%	No., supplement group	%
No. of participants*	1661	50	1657	50
Age at beginning of intervention, y				
<50	537	32	545	33
50-59	743	45	717	43
≥60	381	23	395	24
Sex				
Male	731	44	730	44
Female	930	56	927	56
Cytology in 1983†				
Dysplasia 1	1302	78	1243	75
Dysplasia 2	359	22	414	25
Education				
None	685	41	719	44
Some	968	59	930	56
Tobacco (ever smoke cigarettes regularly >6 mo)				
No	1176	71	1172	71
Yes	477	29	477	29
Alcohol (any use past 12 mo)				
No	1359	82	1328	81
Yes	294	18	321	19
Pickled vegetable (any use past 12 mo in winter or spring)				
No	1484	90	1481	90
Yes	169	10	168	10
Moldy food (any use past 12 mo)				
No	1321	80	1333	81
Yes	332	20	316	19
Family history of esophageal/stomach cancer				
No	958	58	947	57
Yes	695	42	702	43

*Data missing on 16 participants for education, tobacco, alcohol, pickled vegetables, moldy food, and family history.

†P = .02 for difference in distribution of dysplasia category by treatment group.

Among the cancer deaths, 148 (84%) were due to esophageal/gastric cardia cancer, with 82 occurring in the esophagus and 66 in the gastric cardia. There were 11 cancer deaths attributed to tumors elsewhere in the stomach, and

Table 3. Dysplasia trial compliance assessed biochemically over 6-year intervention

	Baseline*						During intervention						
	Placebo			Supplement			Placebo			Supplement			
Analyte	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	No.	Mean	SD	P value†
Retinol, µg/dL of plasma	47	40.65	14.36	46	42.71	13.64	216	40.72	13.42	209	63.05	17.59	.0001
Riboflavin, EGR activation coefficient‡	50	1.69	0.27	45	1.67	0.29	293	1.53	0.35	284	1.13	0.23	.0001
Ascorbic acid, mg/dL of plasma	45	0.60	0.44	43	0.62	0.54	283	0.63	0.41	281	0.92	0.40	.0001
Beta carotene, µg/dL of plasma	47	10.26	5.17	46	10.73	6.10	216	11.41	15.87	209	119.06	86.83	.0001

*Baseline nutritional assessment conducted in September 1984; values adjusted for season.

†P values are from t tests of difference between placebo and supplement during intervention.

‡EGR = erythrocyte glutathione reductase. Lower EGR coefficient indicates higher riboflavin status.

Table 4. Numbers, rates, and RRs of death by cause among those receiving vitamin/mineral supplementation versus placebo

	Placebo		Supplement			
Cause of death	No. of deaths	Rate*	No. of deaths	Rate*	RR†	95% CI
Total	167	17.4	157	16.3	0.93	0.75-1.16
Cancer	89	9.3	87	9.0	0.96	0.71-1.29
Esophageal	44	4.6	38	3.9	0.84	0.54-1.29
Stomach	35	3.6	42	4.4	1.18	0.76-1.85
Cardia	32	3.3	34	3.5	1.04	0.64-1.69
Noncardia	3	0.3	8	0.8	2.68	0.71-10.11
Esophageal/cardia	76	7.9	72	7.5	0.92	0.67-1.28
Other	10	1.0	7	0.7	0.71	0.27-1.87
Cerebrovascular	35	3.6	22	2.3	0.62	0.37-1.06
Other	43	4.5	48	5.0	1.12	0.74-1.69

*Rate per 1000 person-years.

†RR adjusted for age, sex, commune, and initial grade of dysplasia.

other types of cancer accounted for the remaining 17 cancer deaths.

Table 4 also shows the numbers and rates of deaths by cause in the supplement and placebo groups. Esophageal/gastric cardia cancer mortality was 8% less (RR = 0.92; 95% CI = 0.67-1.28) and total mortality 7% less (RR = 0.93; 95% CI = 0.75-1.16) in those taking vitamins/minerals, but neither these nor any of the cause-specific rates differed significantly by group. The RR of total cancer mortality in the vitamin/mineral group was 0.96 (95% CI = 0.71-1.29). A larger reduction in esophageal cancer (RR = 0.84; 95% CI = 0.54-1.29) was countered by an increased rate of stomach cancer (RR = 1.18; 95% CI = 0.76-1.85). The most marked effect was a nearly significant (P = .08) 38% reduction (RR = 0.62; 95% CI = 0.37-1.06) in mortality from cerebrovascular disease. Trends in total and cancer mortality rates over the 6-year intervention period for the treatment versus placebo groups are shown in Figs. 1 and 2.

A total of 448 incident cancers were diagnosed during the 6-year intervention. As indicated in Fig. 3, nearly half of all cancers were diagnosed during the cytologic and endoscopic screenings of 1987 and 1991. As shown in Table 5, total cancer incidence was similar in the treatment and placebo groups (RR = 1.01; 95% CI = 0.84-1.22), as was incidence for esophageal/gastric cardia cancer (RR = 0.98; 95% CI = 0.81-1.19). The incidence of esophageal cancer was lower and stomach cancer higher in the group receiving multiple vitamin/mineral supplementation, but these differences were not significant (P>.10).

Discussion

The participants randomly assigned to the treatment group in this study received 6 years of daily supplementation with multiple vitamins and minerals at doses high enough to correct deficiencies and provide adequate supplies of each nutrient. In this group, esophageal/gastric cardia cancer mortality was 8% lower and overall mortality 7% lower compared with the placebo group. The decreases were not statistically significant. A sizable reduction of borderline significance, however, was seen in cerebrovascular disease mortality.

The trial in Linxian among individuals with esophageal dysplasia offered several advantages as a test of the effectiveness of vitamin/mineral supplementation on the late stages of esophageal/gastric carcinogenesis. Prior to the trial, the population under study was slightly deficient in a number of nutrients postulated to play a role in esophageal and gastric cancer and suffered some of the world's highest rates of these cancers (*1,8-11*). Although potential protective effects were thought to exist for a number of micronutrients, including retinol, beta carotene, riboflavin, niacin, ascorbic acid, vitamin E, magnesium, molybdenum, selenium, and zinc (*16-24*), the population of individuals with esophageal dysplasia was not large enough for separate evaluation of these compounds. As a result, the multiple vitamin/mineral supplementation approach was adopted. The inclusion of a wide variety of vitamins and minerals increased the trial's sensitivity to detect benefits if any of 26 different nutrients were cancer inhibitors. The number of end points achieved in the trial was relatively large, and the CIs in Table 4 indicate that reductions in total mortality and cancer mortality from the vitamin/mineral supplementation are no greater than 25% and 29%, respectively. Aiding assessment of outcomes was the stability of the population and its willingness to participate in the multiyear effort, which ensured almost complete follow-up. Compliance as judged by pill disappearance (implying pill ingestion) and by biochemical means was also high. Finally, the reliability of the cancer diagnoses was ensured by standardized reviews of diagnostic materials by American and Chinese experts in alimentary tract tumors.

Several limitations of the study must be considered in interpreting the findings. All participants had been cytologically diagnosed before the start of the intervention with esophageal dysplasia, a lesion conferring a risk of esophageal cancer even greater than the very high risk prevailing in the Linxian general population (*3*). It may be that the intervention came too late, since it is possible that individuals with dysplasia are less amenable to a potential cancer benefit of nutrient supplementation than those without dysplasia. Also, the doses of the vitamins and minerals may not have been sufficiently high, although they were shown to raise blood concentrations of measured substances well into

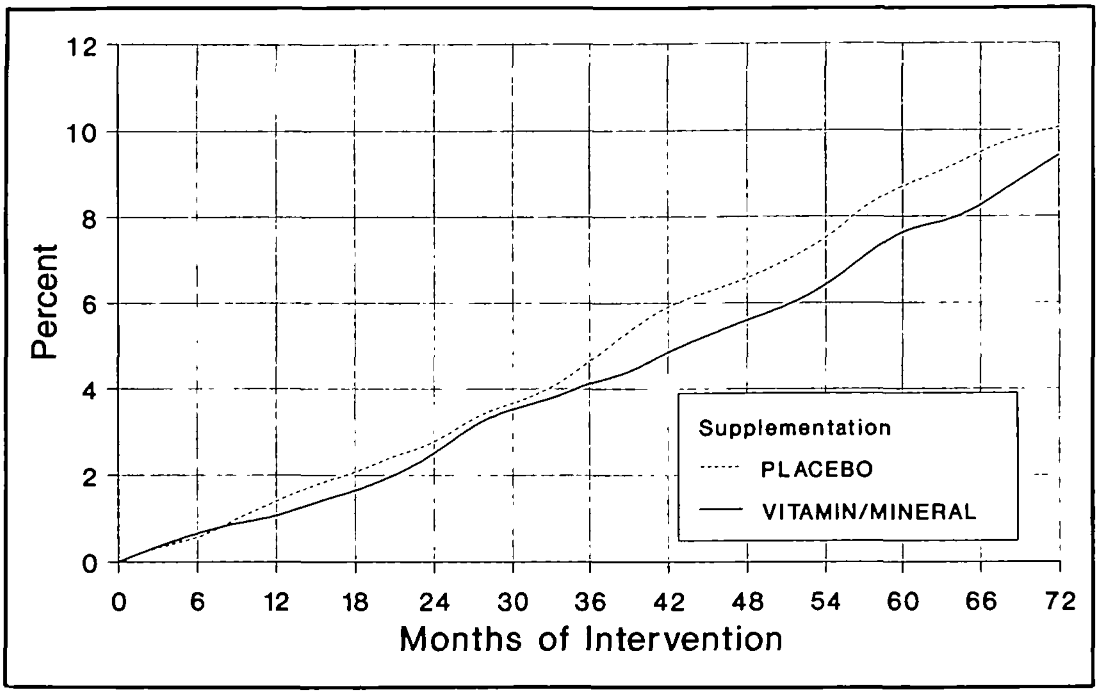

Fig. 1. Cumulative total deaths as percent of esophageal dysplasia trial study population, May 1985-May 1991.

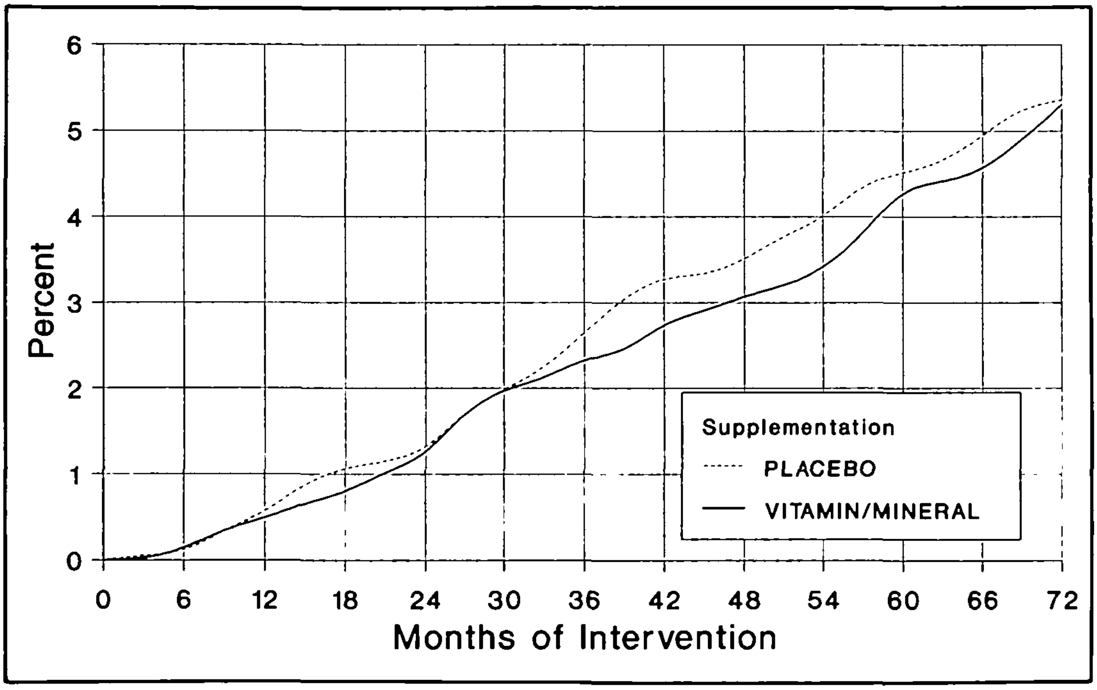

Fig. 2. Cumulative total cancer deaths as percent of esophageal dysplasia trial study population, May 1985-May 1991.

adequate ranges for normal health. We kept the doses of most of the vitamins and minerals at less than or equal to three times U.S. RDAs to avoid competitive antagonism between compounds, but it is possible that potential benefits of one vitamin or mineral may have been hindered by the presence of others. Evidence of such interactions has been reported in both animals (*25*) and humans (*26*). Finally, and perhaps most importantly, the intervention and/or follow-up periods may not have been long enough to detect significant benefits. Additional follow-up over the coming years is planned to assess longer-term effects on cancer incidence and mortality from cerebrovascular diseases and other diseases.

In the larger parallel trial in the Linxian general population described in this issue of the Journal (*13*), the effectiveness of four specific vitamin/mineral combinations was evaluated. Total mortality during the 1986-1991 intervention period was reduced by 9% and cancer mortality by 13% among those receiving daily supplements of beta carotene, vitamin E, and selenium. These differences were significant ($P \leq .05$) because of the large study size, with nearly 15000 persons receiving and 15000 not receiving

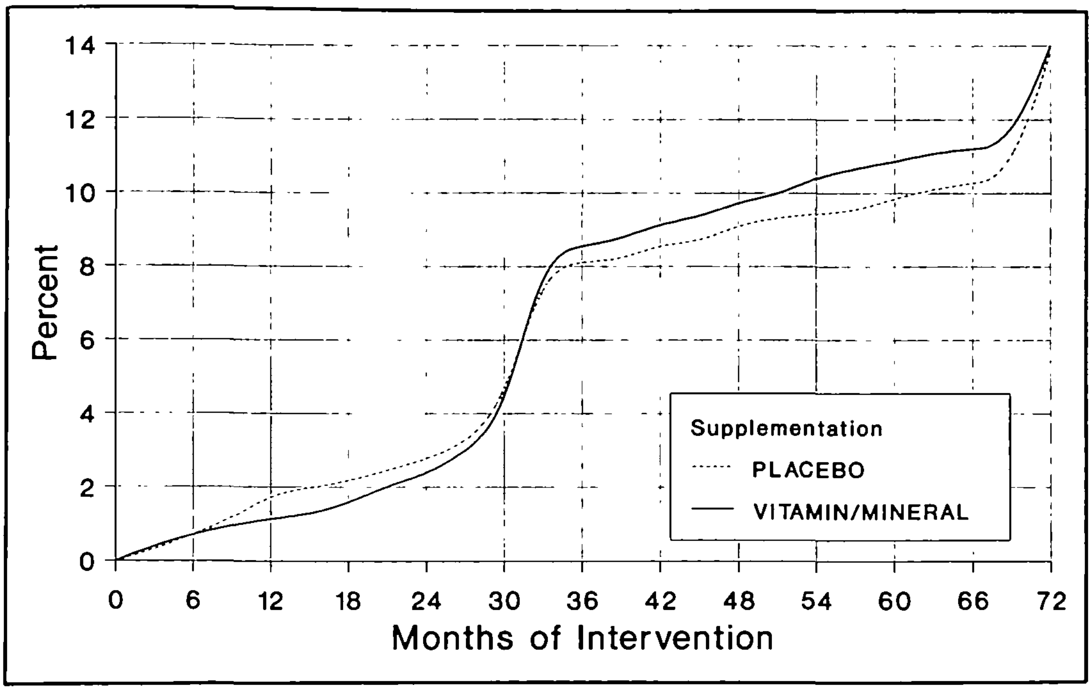

Fig. 3. Cumulative total cancer incidence as percent of esophageal dysplasia trial study population, May 1985-May 1991.

these supplements. Given the wide CIs for the RRs in the dysplasia trial, the findings from the two trials can be considered fairly consistent. The slightly greater (and more significant) effects observed in the general population trial, however, may reflect true differences in biologic response between participants in the two trials. Essentially similar physiologic doses of vitamins and minerals were used for nearly similar durations in both trials. More severe lesions, however, such as those required for entry into the dysplasia trial, occur later in carcinogenesis and may simply require stronger inhibitors or longer durations of inhibition to show meaningful efficacy.

Although not an element of the hypothesis at the onset of this study, the most marked reduction in death rates among those receiving vitamins and minerals occurred for cerebrovascular disease, which was second to cancer as a cause of death in Linxian. The statistically suggestive ($P = .08$ with a two-sided test) result is biologically plausible in view of reports from observational studies (*7,27-30*) indicating that antioxidants and certain other vitamins and minerals may lower the risk of stroke and its major risk factor, hypertension. Mild though insignificant protective effects for several of the nutrient combinations in cerebrovascular disease mortality were also observed in the general population trial (*13*). However, it must be kept in mind that the CIs for the reduced risk of cerebrovascular disease mortality in the treatment group were wide, and it is premature to conclude that any of these substances may lower risk.

In summary, our trial results suggest little initial benefit in cancer incidence or mortality during the 6 years of vitamin/mineral intervention among persons with esophageal dysplasia. However, there was a small reduction in total mortality, due mainly to a sizable decline in deaths from cerebrovascular diseases. Additional follow-up of the trial participants subsequent to intervention will help us assess whether these trends persist and if longer-term benefits of vitamin and mineral supplementation emerge.

Table 5. Numbers, rates, and RRs of cancer incidence among those receiving vitamin/mineral supplementation versus placebo

	Placebo		Supplement			
Type of cancer	No. of cancers	Rate, %*	No. of cancers	Rate, %*	RR†	95% CI
Total	221	13.3	227	13.7	1.01	0.84-1.22
Esophageal	128	7.7	123	7.4	0.94	0.73-1.20
Stomach	81	4.9	96	5.8	1.17	0.87-1.58
Cardia	77	4.6	82	5.0	1.05	0.77-1.43
Noncardia	4	0.2	14	0.8	3.54	1.17-10.76
Esophageal/cardia	205	12.3	205	12.4	0.98	0.81-1.19
Other	12	0.7	8	0.5	0.67	0.28-1.65

*Cumulative incidence.

†RR adjusted for age, sex, commune, and initial grade of dysplasia.

References

(*1*) Li JY: Epidemiology of esophageal cancer in China. Natl Cancer Inst Monogr 62:113–120, 1982

(*2*) Shen Q, Liu SF, Dawsey SM, et al: Cytologic screening for esophageal cancer: results from 12877 subjects from a high-risk population in China. Int J Cancer 54:185–188, 1993

(*3*) Dawsey SM, Yu Y, Taylor PR, et al: Esophageal cytology and subsequent risk of esophageal cancer: a prospective follow-up from Linxian, China. Acta Cytologica. In press

(*4*) Li JY, Ershow AG, Chen ZJ, et al: A case–control study of the esophagus and gastric cardia in Linxian. Int J Cancer 43:755–761, 1989

(*5*) Yu Y, Taylor PR, Li JY, et al: Retrospective cohort study of risk factors for esophageal cancer in Linxian, China. Cancer Causes Control 3:205–208, 1993

(*6*) Steinmetz KA, Potter JD: Vegetables, fruit and cancer. I. Epidemiology. Cancer Causes Control 2:325–357, 1991

(*7*) National Research Council: Diet and Health: Implications for Reducing Chronic Disease Risk. National Academy Press, Washington, DC, 1989

(*8*) Zheng SF, Ershow AG, Yang CS, et al: Nutritional status in Linxian, China: effects of season and supplementation. Int J Vitam Nutr Res 59:190–199, 1989

(*9*) Yang CS, Miao J, Yang W, et al: Diet and vitamin nutrition of the high esophageal cancer risk population in Linxian, China. Nutr Cancer 4:154–164, 1982

(*10*) Yang CS, Sun Y, Yang Q, et al: Vitamin A and other deficiencies in Linxian, a high esophageal cancer incidence area in northern China. JNCI 73:1449–1453, 1984

(*11*) Thurnham DI, Zheng SF, Muñoz N, et al: Comparison of riboflavin, vitamin A, and zinc status of Chinese populations at high and low risk for esophageal cancer. Nutr Cancer 7:131–143, 1985

(*12*) Li B, Taylor PR, Li JY, et al: Linxian nutrition intervention trials: design, methods, participant characteristics, and compliance. Ann Epidemiol. In press

(*13*) Blot WJ, Li JY, Taylor PR, et al: Nutrition intervention trials in Linxian, China: supplementation with specific vitamin/mineral combinations, cancer incidence, and disease-specific mortality in the general population. J Natl Cancer Inst 85:1483–1492, 1993

(*14*) US Recommended Daily Allowances: Fed Register 41:46175, October 19, 1976

(*15*) Breslow NE, Day NE: Statistical methods in cancer research. II. The Design and Analysis of Cohort Studies. IARC Sci Publ No. 82. Lyon: IARC, 1987

(*16*) Sporn MB, Newton DL: Chemoprevention of cancer with retinoids. Fed Proc 38:2528–2534, 1979

(*17*) Peto R, Doll R, Buckley JD, et al: Can dietary beta-carotene materially reduce human cancer rates? Nature 290:201–208, 1981

(*18*) Foy H, Mbaya V: Riboflavin. Prog Food Nutr Sci 2:357–394, 1977

(*19*) Shamberger RJ: Vitamins and cancer: current controversies. Cancer Bull 34:150–154, 1982

(*20*) Shklar G: Oral mucosal carcinogenesis in hamsters: Inhibition by vitamin E. JNCI 68:791–797, 1982

(*21*) Blondell JM: The anticarcinogenic effect of magnesium. Med Hypotheses 6:863–871, 1980

(*22*) Luo XM, Wei HJ, Yang SP: Inhibitory effects of molybdenum on esophageal and forestomach carcinogenesis in rats. JNCI 71:75–80, 1983

(*23*) Medina D: Selenium and murine mammary tumorigenesis. Cancer Bull 34:162–164, 1982

(*24*) van Rensburg SJ: Advances in experimental cancer of the esophagus. S Afr Cancer Bull 25:66–76, 1981

(*25*) Ip C: Interaction of vitamin C and selenium supplementation in the modification of mammary carcinogenesis in rats. JNCI 77:299–303, 1986

(*26*) Xu MJ, Plezia PM, Alberts DS, et al: Reduction in plasma or skin alpha-tocopherol concentration with long-term oral administration of beta-carotene in humans and mice. J Natl Cancer Inst 84:1559–1565, 1992

(*27*) Acheson RM, Williams DR: Does consumption of fruit and vegetables protect against stroke? Lancet 1:1191–1193, 1983

(*28*) Salonen JT: Dietary fats, antioxidants and blood pressure. Ann Med 23:295–298, 1991

(*29*) Bulpitt CJ: Vitamin C and blood pressure. J Hypertens 8:1071–1075, 1990

(*30*) Ceriello A, Giugliano D, Quatraro A, et al: Anti-oxidants show an anti-hypertensive effect in diabetic and hypertensive subjects. Clin Sci 81:739–742, 1991

Notes

Affiliations of authors: J.-Y. Li, B. Li, G.-Q. Wang, W. Guo, S.-F. Liu, W. Wang, X.-N. Zou, Y.-P. Wu, Cancer Institute, Chinese Academy of Medical Sciences, Beijing, People's Republic of China.

P. R. Taylor, S. Dawsey, S. D. Mark, P. Greenwald, W. J. Blot, National Cancer Institute, Bethesda, Md.

A. G. Ershow, National Heart, Lung and Blood Institute, Bethesda, Md.

C. S. Yang, Rutgers University, Piscataway, N.J.

Q. Shen, Henan Medical University, Zhengzhou, People's Republic of China.

Correspondence to: William J. Blot, Ph.D., Biostatistics Branch, Division of Cancer Etiology, National Cancer Institute, 6130 Executive Blvd., Rockville, MD 20852.

We thank the Linxian residents who participated in the trials and the Linxian County government, the Linxian People's Hospital, and the commune hospitals in Yaocun, Rencun, and Donggang for support. For guidance and dedicated field and laboratory work in carrying out the investigation, we thank Drs. Yu Yu, Youhai Sun, Shihxin Lu, Youhui Zhang, Kan Yang, Guangyi Li, Quping Yang, Guchen Yang, and Zhijian Chen of the Cancer Institute, Chinese Academy of Medical Sciences. For expert assistance in data management and processing, we thank Linda Cranston, Jack Cahill, Suzanne Huang Rexing, Linda Lannom, Anell Bond, Eric Mehl, Walter Hufford, Erika Wilson, Shelly Niwa, Cathy Agar, and Andrew Nuland of Westat, Inc. For scientific advice and support, we thank Drs. Joseph F. Fraumeni, Jr., Mitchell Gail, Joseph Tangrea, and B. J. Stone of the National Cancer Institute. For expert advice and review of diagnostic materials, we thank Drs. Klaus Lewin, Roberta Nieberg, Marvin Weiner, and Wilfred Weinstein from the University of California at Los Angeles and Drs. Zheng-Yan Wang and Fu-Sheng Liu from the Cancer Institute, Chinese Academy of Medical Sciences. For expert advice and suggestions during the trials, we thank Dr. Paul Engstrom of the Fox Chase Cancer Center (Philadelphia, Pa.), Dr. Pelayo Correa of the Louisiana State University (New Orleans), and Dr. Stephen Lagakos of the Harvard School of Public Health (Boston, Mass.), who served on the Data Safety and Monitoring Committee. We also acknowledge and thank Lederle Laboratories, Inc., and Hoffmann-La Roche, Inc., for their assistance in the provision of the vitamin/mineral supplements.

Manuscript received February 19, 1993; revised June 22, 1993; accepted June 29, 1993.

Call 1-800-SOS-RADON to
get your Radon test information.

EPA Ad Council